REMARKS/ARGUMENTS

With entry of this amendment, claims 1, 2, 6-8, 11, 12, and 14-17 are pending in the instant application. In order to further expedite prosecution of the instant application, claim 32 has been canceled without prejudice or disclaimer. In view of the cancellation of claim 32 and the remarks set forth herein, reconsideration of the instant application is respectfully requested.

Claim rejections under 35 U.S.C. § 112, first paragraph

Claim 32 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled by the specification. While Applicants disagree with this rejection for at least the reasons previously of record, this rejection is obviated by Applicants' cancellation of claim 32 as set forth above. Applicants reserve the right to pursue the subject matter of claim 32 in a related, co-pending application.

Claim rejections under 35 U.S.C. § 103

Claims 1, 2, 6-8, 11, 12, and 14-17 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over U.S. Patent No. 5,942,607 in view of Kaufman *et al.*; statements in the specification on page 37 at lines 7-18; Rock *et al.*; U.S. Patent No. 5,738,852; WO 98/04705 and the CAPLUS Accession No. 1998: 106018 summary of WO 98/04705; U.S. Patent No. 6,338,947; U.S. Patent No. 6,045,802; and Harlow and Lane (*Antibodies: A Laboratory Manual* 1988, p. 104). This rejection is essentially the same as set forth in previous office actions. With the present rejection, the Examiner additionally cites to p. 104 of Harlow and Lane as teaching that "subcutaneously injected immunogens will drain quickly into the local lymphatic system and become concentrated in the lymph nodes closest to the injected sites." (Office Action dated 4/19/06 at p. 7.) The Examiner contends that this teaching of Harlow and Lane provide an additional motivation to administer peptide antigen and B7-encoding vector separately at closely adjacent sites, as required by the present claims.

Applicants traverse the instant rejection. For the reasons set forth herein below, in addition to reasons previously of record, a case of obviousness under § 103 has not been established with respect to the present claims. In particular, to further show non-obviousness of the claimed method, Applicants submit herewith the Declaration of Jay Berzofsky under 37 C.F.R. § 1.132 (hereinafter the "Berzofsky Declaration"), which addresses the Examiner's remarks in the Office Action and shows that the cited references would not lead one of skill in the art to the present invention. As shown by the Berzofsky Declaration and as further discussed herein, the cited references do not provide a sufficient motivation to the skilled artisan to achieve the claimed invention. Nor do these references provide either a reasonable expectation of success or a suggestion of all limitations recited in the pending claims.

Initially, Applicants note that a *prima facie* case under 35 U.S.C. § 103 requires a clear and particular showing, in the prior art, of a motivation sufficient to impel one to do specifically what applicant has done. The Examiner must show, *inter alia*, some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify a reference or combine reference teachings so as to achieve the specific combination as claimed by the applicant. *See* MPEP at §§ 2142 and 2143.01; *In re Fine*, 5 USPQ2d 1596, 1598, 1599 (Fed. Cir. 1988); *In re Dance*, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998). The suggestion or motivation to make the claimed combination must be found in the prior art and cannot be based on applicant's disclosure. MPEP § 2142. *See also* MPEP §§ 2143 and 2143.01 (citing cases). Moreover, the proposed motivation must have sufficient "force" to "impel persons skilled in the art to do what applicant has done." *Ex parte Levengood,* 28 USPQ2d 1300, 1302 (Bd. Pat. App. Inter. 1993). The motivation must also be both objective and specific, *i.e.*, the Examiner's showing must be clear and particular. *See In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). It is this requirement for evidence of particularized motivation that provides a safeguard against the "tempting but forbidden zone of hindsight." *Id.* at 1616.

Moreover, in addition to showing a clear and particular motivation, the Examiner must also show a reasonable expectation of success with respect to the claimed invention, as well as a teaching or suggestion of all claim limitations. MPEP § 2142. As with the motivation to

modify or combine reference teachings, a reasonable expectation of success and all claim limitations must be found in the prior art. *See id.*

In the present case, Applicants submit that a *prima facie* case of obviousness has not been established with respect to the instant claims because (a) the cited references, whether alone or combined, do not teach or suggest separate administration of a peptide antigen and B7-encoding vector to closely adjacent sites; (b) a reasonable expectation of success for inducing an immune response using this administration mode has not been shown in the art; and (c) a clear and particular motivation, sufficient to impel the skilled artisan to achieve the claimed invention, has not been established. Each of these points is addressed below in the specific context of the Examiner's remarks in the Office Action.

First, to address the Examiner's remarks regarding Shirai *et al.*, the Shirai reference, while pertaining to studies of Th and CTL epitopes, provides evidence that there would not be a reasonable expectation in the art that two agents, administered separately to closely adjacent sites, would have sufficient access to the same cells to achieve a corresponding physiological result. Shirai *et al.* describe peptide vaccine studies in which Th and CTL epitopes were administered either as an admixture of non-linked epitopes or as a single peptide with the Th and CTL epitopes covalently linked. (Berzofsky Declaration at ¶9.) The studies of Shirai *et al.* show that any CTL response is very poor if the Th and CTL epitopes are not coupled. (*Id.*) With regard to the Examiner's statements that Shirai *et al.* also teaches two studies in which covalent linkage of Th and CTL epitopes was not obligatory for inducing a CTL response *in vivo*, it is understood that the Examiner is referring to statements in the last paragraph of page 552 of the reference, in which Shirai *et al.* refer to two previous studies in which Th and CTL epitopes were not covalently linked. (*Id.* at ¶10.) Shirai *et al.*, however, reconcile these previous studies with their own covalent linkage study. Specifically, Shirai *et al.* note that in one of the previous studies, the Th and CTL determinants were physically together within the same microdroplets of an adjuvant emulsion, and in the other study, the inherent disadvantage of an unlinked mixture was overcome by multiple high doses of peptide. Shirai *et al.* further note that these results are consistent with the requirement for proximity or presentation on the same presenting cell. (*Id.*)

In view of the above, the skilled artisan reading Shirai *et al.* would understand this reference as teaching that CTL responses are poor if the Th and CTL determinants are either (1) not coupled (*e.g.*, physically in a microdroplet or covalently) or (2) if unlinked, administered at a high dose (*e.g.*, high concentration) in an admixture. (Berzofsky Declaration at ¶11.) Further, although the Shirai *et al.* study deals with two peptides rather than a peptide and a DNA molecule, the skilled artisan would understand Shirai *et al.* as demonstrating, *inter alia*, the basic principle that, unless two molecules are linked or administered together at high doses, there is not a reasonable expectation that these agents will be sufficiently accessible to the same cell when administered *in vivo* to effect a corresponding physiological response. (*Id.* at ¶12.) In particular, the skilled artisan would not have a reasonable expectation that two molecules (including, as in the present case, two molecules where one is a nucleic acid and the other is a protein or peptide antigen), administered separately to an individual at closely adjacent sites, would be taken up by the same cell. At least to this extent, the skilled artisan would regard Shirai *et al.* as relevant to the consideration of whether separately administered peptide and nucleic acid would be sufficiently accessible to the same antigen presenting cells *in vivo* to effect an immune response. (*Id.*)

Moreover, with respect to the Examiner's statements regarding the draining of immunogens to the lymph nodes, as noted in the specification, direct injection of DNA into vertebrate tissues had been shown to result in the uptake and expression of the DNA. (Berzofsky Declaration at ¶13, citing the '310 application at p. 37, ll. 11-14.) It was also known as of the application's filing date, however, that DNA typically transfects the cells immediately at the site of injection. (Berzofsky Declaration at ¶13.) The same is not necessarily true of peptide immunogens, which are typically taken up by specialized antigen presenting cells that then migrate to the draining lymph nodes to present antigen to T cells. At least because of this difference in the way nucleic acids and peptide antigens are taken up by cells following injection (and in addition to the importance of coupling of agents as demonstrated by Shirai *et al.*), the skilled artisan would not reasonably expect nucleic acid and peptide, separately administered at closely adjacent sites, to reach the same cells to effect a corresponding physiological response. (*Id.*)

This understanding in the art is consistent with the teachings of the references cited in the Office Action. (Berzofsky Declaration at ¶14.) US 5,942,607 ("Freeman *et al.*") suggests to the skilled artisan sequential *in vitro* transfection of cells with B7 DNA and pulsing with peptide, followed by introduction of these cells into the host mammal. This method does not teach or suggest separate administration of two agents *in vivo*, and avoids the perceived disadvantage of such separate administration as discussed above. Moreover, the fact that Freeman *et al.* make the effort to transfect the cells would imply to someone of skill in the art that it was not expected that injection of these agents at separate sites would be effective. (*Id.*)

Further, none of the other references cited in the Office Action would suggest to the skilled artisan to administer Freeman *et al.*'s B7 DNA and peptide antigen separately at closely adjacent sites *in vivo*. (Berzofsky Declaration at ¶15.) At the time of filing of the instant application, for *in vivo* administration of two separate agents targeting the same cell, it was typical to use the agents together as an admixture, rather than as individual formulations administered separately. (*Id.* at ¶16.) Accordingly, in the absence of any specific teaching or suggestion to the contrary, and assuming (for argument's sake) a general teaching of *in vivo* administration, one of skill in the art would be led to administer Freeman's B7 DNA and peptide antigen molecules together as an admixture, or coupled, but not separately. (*Id.*) In the present case, none of the cited references teach or suggest to the skilled artisan the administration of two agents separately at closely adjacent sites (*id.* at ¶17), and if anything suggest administration of agents as an admixture or coupled, as further summarized below:

> In Kaufmann *et al.*, B7.1 DNA is introduced into HPV E7 antigen expressing cervical carcinoma cells (*i.e.*, into cells already expressing target peptide antigen) *in vitro*. (Berzofsky Declaration at ¶18.) Because Kaufmann *et al.* targets cells already expressing antigen, Kaufmann *et al.* do not address *co*-administration of B7.1 DNA and antigenic peptide. Nor do Kaufmann *et al.* address issues pertaining to *in vivo* administration. Indeed, the fact that Kaufmann *et al.* transfect cells already expressing antigen would imply to someone of skill in the art that it was not expected that injection of these agents at separate

sites would be effective, but rather that the antigen and B7.1 need to be expressed in the same cell. (*Id.* at ¶18.)

Rock *et al.* pertains to an analysis of the optimal length of CTL peptides for binding to MHC class I molecules and does not even address introduction of B7 DNA into cells. (*Id.* at ¶19.)

US 5,738,852 ("Robinson *et al.*") discusses administration of polynucleotides encoding a co-stimulatory molecule and polypeptide antigen. (Berzofsky Declaration at ¶20.) Robinson states that the sequences encoding the co-stimulatory molecule and peptide antigen can be on separate polynucleotides, but "preferably are on the same polynucleotide" (*see* col. 10, ll. 36-39). Moreover, for *in vivo* administration, Robinson again points to a single polynucleotide encoding both polypeptides as preferred (*see* col. 13, ll. 41-48). Robinson does not specifically address how to administer separate polynucleotides encoding co-stimulatory molecule and peptide antigen. In particular, nowhere does Robinson teach or suggest to the skilled artisan *in vivo* administration of two polynucleotides separately at closely adjacent sites for achieving expression of B7 and peptide antigen in an APC. In light of the art-recognized mode for administering agents targeting the same cell as an admixture, Robinson would suggest to the skilled artisan administration of individual polynucleotides (encoding co-stimulatory molecule and peptide antigen) as an admixture, and not separately. (Berzofsky Declaration at ¶20.)

WO 98/04705 ("Balloul *et al.*") discusses a composition comprising HPV polypeptides and B7.1, or one or more vectors encoding these polypeptides. (Berzofsky Declaration at ¶21.) Balloul's discussion of HPV antigen and B7.1, or vectors encoding these, as components of a

"composition" would suggest to the skilled artisan the use of these agents as an admixture. Balloul does not teach or suggest to the skilled artisan *in vivo* administration of these polypeptides or vectors separately at closely adjacent sites. (*Id.* at ¶21.)

US 6,338,947 ("Sahin *et al.*") discusses pharmaceutical formulations that combine antigenic peptides, or DNA encoding antigenic peptides, with co-stimulatory molecules. (Berzofsky Declaration at ¶22.) Sahin's brief reference to combining antigen with co-stimulatory molecules, which is in the specific context of "formulations" for administering peptide antigen (*see* Sahin at col. 12, ll. 17-21), suggests to the skilled artisan the use of peptide antigen (or encoding DNA) with co-stimulatory molecule as an admixture. Sahin *et al.* does not teach or suggest to the skilled artisan *in vivo* administration of the co-stimulatory molecules and antigenic peptides separately at closely adjacent sites. (Berzofsky Declaration at ¶22.)

US 6,045,802 ("Schlom *et al.*") discusses an admixture of a recombinant vaccinia virus (rV) expressing a tumor-associated antigen and an rV expressing B7. (Berzofsky Declaration at ¶23.) Schlom *et al.* do not teach or suggest to the skilled artisan *in vivo* administration of the rV encoding antigen and rV encoding B7 separately at closely adjacent sites. (*Id.*)

Harlow and Lane discuss migration of subcutaneously injected immunogens to the draining lymph nodes closest to the site of injection, but does not address co-administration of DNA with peptide antigens, whether as an admixture or separately. (*Id.* at ¶24.)

In view of the above, the cited references, whether taken alone or in any combination, do not teach or suggest administration of peptide antigen and B7-encoding nucleic acid separately to closely adjacent sites. (*See* Berzofsky Declaration at ¶¶14 and 15. *See also id.*

at ¶¶16-24.) Accordingly, the cited references do not teach or suggest all claim limitations as recited in the pending claims.

Furthermore, in light of the teachings of Shirai *et al.*, together with the difference in the way nucleic acids and peptide antigens are taken up by cells following injection, and in further view of the lack of any demonstration or discussion in the cited art of administering peptide and vector separately to closely adjacent sites, the skilled artisan would not have a reasonable expectation of success with respect to the presently claimed invention, without the benefit of Applicants' disclosure. (*See* Berzofsky Declaration at ¶25.)

With regard to a motivation to combine the cited art, the Examiner asserts the following as proposed motivations to achieve the claimed invention based on the cited references:

(a) in order to enhance a CTL response;

(b) it was desirable to use an adjuvant with peptide antigens (citing Sahin *et al.*);

(c) the immune response that ensues from expression of both antigen and B7 in an APC (citing Robinson *et al.*), together with the knowledge that s.c.-injected immunogens drain into lymph nodes closest to the injection site (citing Harlow and Lane); and

(d) using an admixture of vector encoding antigen and vector encoding B7 can lead to co-infection of, and co-expression in, APCs to enhance T cell response (citing US 6,045,802).

None of the Examiner's proposed motivations are specific enough or have sufficient force to lead one of ordinary skill in the art to the particular invention as presently claimed in the application. (Berzofsky Declaration at ¶27.) The proposed motivations, as enumerated by the Examiner and summarized above, do not specifically lead the artisan to

administration of a peptide antigen and nucleic acid encoding B7 separately at closely adjacent sites (*id.*), for at least the reasons below.

First, regarding "enhancement of a T cell response" as a proposed motivation, the cited references generally show induction of CTL responses without separate administration of agents to closely adjacent sites. (Berzofsky Declaration at ¶28.) Indeed, each of the cited references that pertain to the use of both a peptide antigen and a co-stimulatory molecule discusses a specific and self-sufficient strategy for inducing an immune response. The cited references do not provide any teaching or suggestion as to how separate administration of the disclosed agents to closely adjacent sites would in any way improve the strategies discussed. Therefore, the desire to induce an immune response, by itself, would not provide a specific suggestion to the skilled artisan to modify the references. (*Id.*)

Second, as to a desire "to use an adjuvant with peptide antigens," it was generally well-known to use adjuvants as an admixture with peptide antigens, *i.e.*, as part of the same formulation. (Berzofsky Declaration at ¶29.) Therefore, assuming that a skilled artisan would be impelled to modify the references so as to use a B7-encoding nucleic acid as an adjuvant with peptide antigen for *in vivo* administration, the skilled artisan reading the cited references would be led to use these agents as an admixture, and not for separate injection. (*Id.*)

Third, regarding the Examiner's reference to the knowledge that s.c.-injected immunogens drain into lymph nodes closest to the injection site, this knowledge does not suggest to the skilled artisan any particular advantage in separate *in vivo* administration of peptide antigen and B7-encoding vector, particularly in view of (i) Robinson's teaching that it is preferred to use a single polynucleotide encoding both co-stimulatory molecule and antigen; (ii) Robinson's silence on the issue of how to administer separate polynucleotides, together with the art-recognized mode for administering agents targeting the same cell as an admixture; and (iii) the teachings or suggestions in other references cited by the Examiner (*e.g.*, Balloul *et al.*, Sahin *et al.*, Schlom *et al.*) pointing to *in vivo* administration of two agents either coupled or as an admixture. (Berzofsky Declaration at ¶30.)

Fourth, with respect to the Examiner's reference to US 6,045,802 (as discussing the use of an admixture of vector encoding antigen and vector encoding B7 for co-expression in APCs to enhance T cell response), an admixture of polynucleotides encoding antigen and B7 does not teach or suggest to the skilled artisan the use of these agents for separate *in vivo* administration. (Berzofsky Declaration at ¶31.) For clarification purposes, Applicants note that the Examiner, at one point, refers to US 6,045,802 as disclosing "injection of the two molecules separately" (Office Action dated 4/19/06 at p. 8, bottom of first paragraph). Applicants believe that the Examiner is using the term "separately" in reference to the use of two polynucleotides that are not covalently linked on the same vector but still used as an admixture, in light of both the Examiner's acknowledgement that the '802 patent discloses the use of the two polynucleotides as an admixture, as well as the '802 patent's lack of any discussion regarding the administration of the two polynucleotides other than on the same vector or as an admixture.

Furthermore, as previously discussed above, there would not be a reasonable expectation that separately administered peptide antigen and DNA encoding B7 would have sufficient access to the same cells to achieve an immune response. (Berzofsky Declaration at ¶32. *See also id.* at ¶¶12 and 13.) A lack of sufficient access to the same cells *in vivo* would be regarded by the skilled artisan as a disadvantage to the use of separate administration of peptide antigen and B7 nucleic acid to closely adjacent sites. (*Id.* at ¶32.) The art suggests that cells in the immediate region of the injection site take up DNA while peptide can be found well-dispersed from the injection site, such as in the draining lymph nodes. This perceived disadvantage would lead the skilled artisan away from the use of separate administration as presently claimed. (*Id.*)

For the reasons set forth above, the cited references do not render the present claims obvious under 35 U.S.C. § 103. The cited references, whether alone or in any combination, do not teach or suggest administering peptide antigen and B7-encoding nucleic acid separately to closely adjacent sites. In addition, the skilled artisan would not have had reasonable expectation that this administration mode would be successful for inducing an immune response. Further, the references do not provide a specific and objective motivation sufficient to impel the skilled artisan to achieve the invention as presently claimed. For these

reasons, the Office has not shown any of the three basic criteria for establishing a *prima facie* case under 35 U.S.C. § 103, the lack of any one of which is sufficient to show non-obviousness over the cited art. Therefore, Applicants respectfully request withdrawal of the present rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Date: August 21, 2006

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Attachments: Declaration of Jay Berzofsky under 37 C.F.R. § 1.132
Exhibit 1
60769454 v1